PATENT

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re the application of:

Juha-Matti SAVOLA et al.

Serial Number: 10/534,091 Group Art Unit: 1618

Filing Date: May 6, 2005 Examiner: Gembeh, Shirley V.

For: OROMUCOSAL FORMULATION AND PROCESS FOR PREPARING THE SAME

DECLARATION PURSUANT TO 37 C.F.R. § 1.132

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Sir:

I, Juha-Matti SAVOLA, hereby declare as follows:

1. I am one of the co-inventors of the invention disclosed and claimed in this application.

2. I have postgraduate educational training in medicine and pharmacology and a quarter century of research and management experience in medicine, pharmacology, and preclinical and clinical trial design and execution.

a) I received my MD in 1983 from the University of Oulu, Finland, my PhD in 1986 in Pharmacology from the University of Oulu, Finland, and was nominated as an Associate Professor (Docent in Drug Discovery) in 1997 by the University of Turku, Finland.

b) From 1983 – 1988, I was engaged in setting up an extensive selection of in vivo and in vitro models in the field of cardiovascular and CNS pharmacology at Oulu University, Finland.

c) From August 1988 – November 1989, I was a Postdoctoral Fellow at Stanford University and the University of California, San Francisco (UCSF), performing research in the molecular and biochemical pharmacology of the adrenergic alpha-2 and beta receptors, including their hormonal regulation at the receptor protein expression and mRNA and DNA levels.

d) Thereafter, from November 1989 through January 1992, I was a Research Scientist, then Laboratory Head, at Farmos Research, Farmos Group Ltd., Finland. In this role, I established a G-protein coupled receptor (GPCR) screening function to support drug discovery efforts.

e) From January 1992 through August 1997 I was Head of the Department for Drug Design and Screening, at the Orion Corporation, Finland, responsible for computational and pharmacological drug discovery functions of Orion Pharma (excluding those related to the cancer drug discovery).

f) For 9 years, starting August 1997, I was CEO at Juvantia Pharma Ltd., Finland. At Juvantia, I was responsible for designing preclinical and clinical development strategies for fipamezole for treatment of movement disorders in advanced Parkinson's disease. During this time, I contributed to developing fipamezole from "napkin chemistry" to first-in-man studies in two years, reformulating the product, and moving the compound into phase 2a proof-of-concept study in two additional years. During this time, Juvantia conducted clinical studies in Finland, the UK and the US.

g) I am currently Vice President of Development, Fipamezole, at Santhera Pharmaceuticals (Switzerland) Ltd., to which Juvantia licensed fipamezole during my tenure as Juvantia CEO. (Santhera is the current owner of this application.) In this capacity, I continue to oversee as program director design of preclinical and clinical development strategies and building development plans for fipamezole as a therapeutic agent in Parkinson's disease. In particular, I have responsibility for designing and providing medical expertise to the clinical study

protocols and other clinical trial documents [Informed Consent Forms (ICFs), Case Report Forms (CRFs), statistical analysis plans, reports and publications], to the investigator's brochure, Investigational Medicinal Product Dossier (IMPD) and the Investigational New Drug (IND) updates, and to clinical study data analysis and interpretation.

h) I am the author of 47 peer-reviewed scientific papers.

i) My curriculum vitae is attached.

3. I have read the Declaration of Dr. Jürg P. Seiler, filed December 30, 2009, and its Appendices, notably Appendix II, and I agree with its factual assertions and its scientific conclusions.

4. I have also read the Official Action mailed February 25, 2010 ("Official Action"), and do not agree with its factual assertions and scientific conclusions. In this Declaration, I address the scientific and medical errors underlying the Examiner's rejections.

QTc Prolongation Is Independent from Heart Rate

5. The Examiner's statement that "QTc is associated with heart rate" (Official Action, page 5, line 4) is incorrect.

6. The QT interval of an electrocardiogram (the time from the beginning of the QRS complex to the end of the T wave) is a measure of the duration of ventricular depolarization and repolarization. See "The QT-Interval in the Electrocardiogram" beginning on page 3 of Appendix II of Dr. Seiler's Declaration filed December 30, 2009.

7. As commonly known, in a normally functioning heart the QT interval has an inverse relationship to heart rate (the faster the heart rate, the shorter the QT interval). Because heart rate varies widely within an individual from time to time, for assessment purposes the measured QT interval must be corrected by means of one of several-commonly used formulae to a heart rate-independent value, QTc. In short, QTc is the QT interval corrected for heart rate.

8. QTc prolongation is independent from heart rate, and can occur even though heart rate remains unchanged. See paragraph 12 of Dr. Seiler's Declaration.

9. In my opinion, nothing concerning QTc prolongation or the absence thereof can be determined or predicted from the heart rate value (or from a change in heart rate) upon administration of a drug.

One of ordinary skill Cannot Predict Whether Oromucosal Administration of Fipamezole Will or Will Not Prolong QTc From Huupponen

10. The Patent Office argument that Huupponen et al., 58 Clin.Pharmacol.Ther. 506-11 (1995) ("Huupponen") suggests fipamezole can be oromucosally administered without prolonging the QTc interval is incorrect.

11. Huupponen teaches oromucosal administration of atipamezole (a fipamezole analog) increases its bioavailability in comparison to oral administration. However, Huupponen fails to disclose anything about atipamezole's effect, if any, on QT interval or its prolongation. In this regard, the Examiner argues

> [s]ince QTc is associated with heart rate and the rate of the heart is unchanged [in Huupponen], it is therefore reasonable that there is no prolongation of QTc was evident (see entire document).

Official Action, p. 5, lines 4 – 6. There can be nothing "reasonable" about the Examiner's QTc inference because it is based on a mistaken belief that QTc is associated with heart rate. In fact, Huupponen's disclosure that oromucosal administration of atipamezole did not change heart rate is meaningless with respect to QTc prolongation because QT prolongation can be induced at unchanged heart rate, and because QTc is a value corrected for changes in, and thus independent from, heart rate.

12. In my opinion, one of ordinary skill in the art would not assume anything from Huupponen regarding the presence or absence of QTc prolongation upon oromucosal administration of atipamezole because nothing concerning QTc prolongation or the absence thereof can be determined or predicted from heart rate. Moreover, nothing can be predicted regarding the presence or absence of QTc prolongation due to oromucosal administration of fipamezole, an atipamezole analog as to which Huupponen is completely silent.

Those of Ordinary Skill Will Abandon A Drug Candidate which Prolongs QTc

13. The delay in cardiac repolarization caused by QTc prolongation creates an environment which favors ventricular arrhythmias. One of these ventricular arrhythmias is called "Torsade de Pointes", an arrhythmia which can be fatal.

14. QTc prolongation is evaluated as early as possible in the research and development of a new drug molecule precisely because of the risk of fatal arrhythmias. In my opinion, the dosages used are irrelevant because pharmaceutical industry practice is to abandon all further development of a drug molecule which prolongs the QTc interval - at any dose - due to the risk of fatal arrhythmias such as Torsade de Pointes.

The Dog Toxicity Data Can Be Extrapolated to Clinical Dosages

15. International guidelines on how to properly assess a drug's tendency to prolong the QT interval include the recording of cardiac conductivity as electrocardiograms from conscious dogs which have been administered the drug under investigation at

various doses, including multiples of the anticipated human exposure to the drug in the clinic.

16. The dog toxicity studies performed with fipamezole (Application Example 8) show that *oral* administration causes QTc prolongation[1], with the prolongation increasing with increasing fipamezole plasma concentration once the systemic concentration in blood exceeds a certain threshold.

17. As further reported in Example 8, we demonstrated that *oromucosal* administration, remarkably, does not cause QTc prolongation at the relevant plasma concentrations, i.e., the concentrations at which QTc prolongation had been observed upon *oral* administration. For purposes of this second study, the only relevance of dosage was to ensure plasma concentrations equal to and greater than those that cause QTc prolongation upon *oral* administration, in order to permit direct comparison of the relative propensity of the drug to cause QTc prolongation by these two different routes of administration.

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[1]Although the specification states that *un*corrected "QT prolongation was observed", corrected QTc values were also prolonged at those plasma concentrations.

18. In my opinion, one of ordinary skill in the art would extrapolate the QTc data generated in the dog toxicity studies to the clinical situation. More particularly, one of ordinary skill would believe oromucosal administration of fipamezole would not prolong the QTc interval at *any* clinical dose in view of (1) the absence of QTc prolongation at higher-than-clinical dosages when oromucosally administered to the dog, and (2) the dose-dependent nature of QTc prolongation caused by oral administration of fipamezole.

19. All statements made herein of my own knowledge are true and all statements made on information and belief are believed to be true. These statements are made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United

States Code, and that such willful false statements may jeopardize the validity of the application or any patent resulting therefrom.

Signed this 25th day of May, 2010.

Juha-Matti Savola

Enclosure:
Curriculum vitae of Juha-Matti Savola

Curriculum Vitae

Name	Juha Savola
E-mail	juhamatti.savola@gmail.com
Home Address	Rainenweg 130 CH-4135 Reinach BL Switzerland
Telephone	+41 79 460 95 93 (work)
Date of Birth	January 28th, 1958
Nationality	Finnish
Civil status	Married
Resident	Switzerland, Reinach (BL)
Permit status	B
Education	MD, PhD University of Oulu, Finland
Current Position	VP Development Fipamezole Santhera Pharmaceuticals (Switzerland) Ltd. CH-4410 Liestal, Switzerland

Relevant work experience:

Since 2006 (3 years) at current position providing successful clinical and preclinical program development and execution in the leading role;
9 years CEO and head of clinical development at Juvantia Pharma Ltd.

Languages	Good written and spoken English, intermediate in written German
Computer skills	Very good (MS Office, Project, Access, PSNext)

Professional Experience

8.2006-present **Director Clinical Development / VP Development Fipamezole, Santhera, Switzerland**

- Indications: Parkinson's disease, neurogenic orthostatic hypotension
- Program director
  - Designing preclinical and clinical development strategies and building development plans with reporting and budget responsibility
  - Building and leading the cross-functional matrix development team with global responsibility for all development aspects (non-clinical, technical and clinical phases 1 to 3)
  - Designing and providing medical expertise to the clinical study protocols and other clinical trial documents (ICFs, CRF, statistical analysis plans, reports and publications), to the investigator's brochure, IMPD and the IND updates, and to clinical study data analysis and interpretation
  - Developing contents and presentation materials for advisory boards, investigator meetings and for the training of monitors and CRAs

- FJORD (US, India) and FOEHN (France, Portugal) phase 2 studies
- Medical expertise with internal (MT, BOD) and external (health authorities, KOLs and investigators) stakeholders
- Leadership in establishing and maintaining contacts with the clinical community, KOLs and investigators
- Interfacing with drug safety/pharmacovigilance and regulatory functions
- Supporting business development activities

- Member of the Clinical Science Team of Santhera and the Scientific Committee of the Fjord Study

1997-2006 **Chief Executive Officer, heading drug development, Juvantia Pharma Ltd., Finland**

- Indications: Parkinson's disease, chronic pain, schizophrenia, vasoconstrictive disorders
- Planning for the strategic and operative activities of the company, including fundraising and execution of the exit plan, setting up the most advanced high-throughput drug discovery unit in Finland at the time (combination of the efforts of computational chemistry, high-throughput organic chemistry and pharmacological testing) and clinical operations and establishing business development and other administrative corporate functions
  - Building a portfolio of fipamezole, novel non-peptidic somatostatin $SST_{1/4}$ subtype selective agents for chronic pain and inflammatory diseases, alpha-2C selective antagonists for treatment of depression and schizophrenia and alpha-2B antagonist for treatment of vasoconstrictive disorders
  - Development and implementation of product positioning strategies
  - Establishing and maintaining a strong IPR portfolio to support the product concepts
  - Establishing licensing agreements with Orion Corporation and two major leading international pharmaceutical companies
  - Initiating and leading the fipamezole licensing deal arrangement with Santhera
- Designing preclinical and clinical development strategies and building the development plan for fipamezole in treatment of movement disorders in advanced Parkinson's disease
  - Developing fipamezole from napkin chemistry to first-in-man studies in two years, reformulated the product and got into phase 2a proof-of-concept study in two additional years
  - Conducting the clinical studies in Finland, the UK and the US under the FDA IND and regulatory approval process of the national health authorities

1993-1997 **Department Head, Drug Design and Screening, Orion Corporation Orion Pharma, Finland**

- Responsible for the operative functions with budget responsibilities of the computational and pharmacological drug discovery functions of Orion Pharma (excluding those related to the cancer drug discovery), the units being located in the Espoo, Helsinki and Turku regions

1989-1992 **Research Scientist/Laboratory Head, Farmos Research, Farmos Group Ltd., Finland**

- Setting up a GPCR screening function to support drug discovery

1988-1989 **Postdoctoral Fellow, Department of Anesthesia, Stanford University, and Reproductive Endocrinology Center, Department of Obstetrics and Gynecology, UCSF, USA**

- Molecular and biochemical pharmacology of the adrenergic alpha-2 and beta receptors, including their hormonal regulation at the receptor quantity/mRNA and DNA level, receptor cross-talk

1983-1988 **Research Scientist with teaching duties, Oulu University, Finland**

- Setting up an extensive selection of *in vivo* and *in vitro* models in the field of cardiovascular and CNS pharmacology

Membership in Professional Societies

- Society for Neuroscience
- Movement Disorder Society

Publications

- An author to 47 peer reviewed publications in the field of life sciences (molecular pharmacology, in vitro and in vivo pharmacology) and physical sciences (medicinal chemistry)

Patents

- An inventor to 7 patent families protecting new chemical entities, new indications and novel formulations

Hobbies and interest

- Running (marathon), hiking and down-hill skiing

Publications

1: Sallinen J, Höglund I, Engström M, Lehtimäki J, Virtanen R, Sirviö J, Wurster S, Savola JM, Haapalinna A. Pharmacological characterization and CNS effects of a novel highly selective alpha2C-adrenoceptor antagonist JP-1302. Br J Pharmacol. 2007 Feb;150(4):391-402. Epub 2007 Jan 15. PubMed PMID: 17220913; PubMed Central PMCID: PMC2189732.

2: Höglund IP, Silver S, Engström MT, Salo H, Tauber A, Kyyrönen HK, Saarenketo P, Hoffrén AM, Kokko K, Pohjanoksa K, Sallinen J, Savola JM, Wurster S, Kallatsa OA. Structure-activity relationship of quinoline derivatives as potent and selective alpha(2C)-adrenoceptor antagonists. J Med Chem. 2006 Oct 19;49(21):6351-63. PubMed PMID: 17034141.

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4: Engström M, Närvänen A, Savola JM, Wurster S. Assessing activation of the human neuropeptide FF2 receptor with a non-radioactive GTP binding assay. Peptides. 2004 Dec;25(12):2099-104. PubMed PMID: 15572197.

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11: Saleem A, Engström M, Wurster S, Savola JM, Pihlaja K. Interaction of folk medicinal plant extracts with human alpha2-adrenoceptor subtypes. Z Naturforsch C. 2002 Mar-Apr;57(3-4):332-8. PubMed PMID: 12064736.

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alpha2-adrenoceptor agonistic properties. Naunyn Schmiedebergs Arch Pharmacol. 1983 May;322(4):279-85. PubMed PMID: 6135165.

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Patents

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2. Juha-Matti Savola, Paivi Juujarvi, Jukka Ilkka. Oromucosal formulation and process for preparing the same, US Pat. 10534091 - Filed Nov 10, 2003
3. Arto Karjalainen, Paavo Huhtala, Juha-Matti Savola, Siegfried Wurster, Maire Eloranta, Maarit Hillila, Raimo Saxlund, Victor Cockcroft, Arja Karjalainen. Imidazole derivatives having affinity for alpha2 receptors, US Pat. 6313311 - Filed Feb 2, 1999 - Orion Corporation
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